transgenic mice and cells and tissues isolated from said mice may be found, for example, at page 18, lines 22-24, page 19, lines 33-35, page 21, lines 11-22, page 39, lines 28-29 and page 59, lines 18-36 through page 60, line 9 of the specification. Support for claim 49 directed to a transgenic mouse comprising a heterozygous disruption in a retina-specific nuclear receptor gene may be found, for example at page 21, lines 19-22 of the specification. Lastly, support for claim 50 directed to transformed cells may be found, for example, at page 2, lines 29-35 of the specification.

Amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in related applications. Moreover, the amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation or continuation-in-part application.

Upon entry of the amendments, claims 38-50 are pending in the instant application.

II. Rejections

A. Rejection under 35 U.S.C. § 112, first paragraph

Claim 8 was rejected under 35 U.S.C. § 112, first paragraph as not enabling one skilled in the art to make the invention commensurate with the scope of the claim. Applicants respectfully traverse this rejection. However, in view of the cancellation of Claim 8, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is moot.

Claims 17-23 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification, while being enabling for a homozygous retina-specific nuclear receptor knockout mouse lacking production of functional retina-specific nuclear receptor protein, does not reasonably provide enablement for a heterozygous retina-specific nuclear receptor knockout mouse or a retina-specific nuclear receptor gene disrupted mouse. Applicants respectfully traverse this rejection. However, in view of the cancellation of Claims 17-23, the Examiner's rejection under 35 U.S.C. § 112, first paragraph, is moot.

Applicants submit that new claims 38-50 are fully enabled by the teachings of the specification. As the rejection under 35 U.S.C. § 112, first paragraph of claims 8, 17-23 is no longer relevant as a result of the cancellation of these claims, and new claims 38-50 are fully

enabled by the teachings of the specification, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

B. Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-4, 9, 10 and 24 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection. However, as a result of the cancellation of claims 1-4, 9, 10 and 24, the Examiner's rejection is moot. Withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Applicants submit that new claims 38-50 are definite and particularly point out and distinctly claim the subject matter regarded as the invention in accordance with 35 U.S.C. § 112, second paragraph.

C. Rejection under 35 U.S.C. § 103

Claims 1-8 and 10 were rejected as being unpatentable under 35 U.S.C. § 103(a) based upon the teachings of Mansour *et al.*, 1988, *Nature* 366:348-352 ("Mansour") in view of Chen *et al.* 1999, *Proc. Natl. Acad. Sci. U.S.A.* 96(26):15149-15154 ("Chen"). Applicants respectfully traverse this rejection. However, as result of the cancellation of claims 1-8 and 10, the rejection is moot.

New claims 38-50 are non-obvious over the teachings of the prior art references. More particularly, the claimed invention relates to the *in vivo* mammalian characterization of the function of the retina-specific nuclear receptor gene, and provides transgenic animals and cells comprising disruptions in retina-specific nuclear receptor genes and methods and compositions relating thereto, which are not obvious in view of the teachings and disclosures of the references cited by the Examiner.

According to the Examiner, Mansour teaches a strategy for targeted disruption of the *hprt* and proto-oncogene *int-2* in mice embryonic stem cells, and subsequent generation of knockout mice. The disclosure of Mansour specifically relates to a general method for isolating embryonic stem cells containing a targeted mutation in an endogenous gene. More particularly, Mansour teaches the targeted disruption of the *hprt* gene and the proto-oncogene *int-2* in mouse embryonic stem cells by homologous recombination using targeting constructs specific for these genes.

Chen, as characterized by the Examiner, teaches the identification and cloning of a retina-

specific nuclear receptor (RNR) from both human and mouse. The Examiner contends that Chen teaches that RNR is a transcriptional repressor and that RNR interacts with the promoter of CRALBP, a protein involved in the visual cycle.

As described above, the disclosure of Mansour is limited to providing a general approach for isolating embryonic stem cells. As acknowledged by the Examiner, Mansour provides no disclosure or teaching of how to make a retina-specific nuclear receptor gene targeting construct or retina-specific nuclear receptor gene knockout mouse. (See Office Action, page 9). Likewise, Chen provides no teaching or suggestion of creating a targeted disruption in the retina-specific nuclear receptor gene.

Moreover, the disclosures of Mansour and Chen are absent of any teaching or suggestion of disrupting the retina-specific nuclear receptor gene, and in particular, to produce the transgenic mice, targeting constructs, tissues, cells, and methods as recited in the pending claims. More particularly, the teachings of Mansour and Chen combined or alone, do not teach or suggest in any way the transgenic mice comprising disrupted retina-specific nuclear receptor gene, wherein such transgenic mice exhibit eye abnormalities, methods of producing such transgenic mice, targeting constructs, tissues and cells that are related to a disrupted retina-specific nuclear receptor gene as claimed by the present invention.

As the obviousness rejection is no longer relevant as result of the cancellation of claims 1-8 and 10, and new claims 38-50 are not obvious in view of the teachings of Mansour and Chen, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103.

It is believed that the claims are in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-125.

Respectfully submitted,

Date: 7/11/02

Marlette A. Lapiz

Marlette A. Lapiz (Reg. No. 44,202)
DELTAGEN, INC.
740 Bay Road, Redwood City, CA 94063
(650) 569-5100

Enclosures